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JEWELFISH is a multicenter trial ongoing globally.

JEWELFISH: Safety and pharmacodynamic data in non-naïve patients with spinal muscular atrophy (SMA) receiving treatment with risdiplam (RG7916)

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Background

- Spinal muscular atrophy (SMA) is a severe, progressive, inherited neuromuscular disease leading to loss of motor function and reduced life expectancy.¹

- SMA is caused by reduced levels of the survival of motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene.¹,²
  - A second SMN gene, SMN2, produces only low levels of functional SMN protein.³

- Increasing preclinical evidence indicates that SMA is a multisystem disease.⁴
  - Therapies that increase SMN protein levels systemically may have broader therapeutic benefit than those targeting motor neurons alone.

- Risdiplam (RG7916) is a centrally and peripherally distributed oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein.⁵,⁶
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Study design

- JEWELFISH (NCT03032172)7 is an ongoing, multicenter, open-label study to assess the safety, tolerability and PK/PD relationship of once-daily oral administration of risdiplam in patients aged from 6 months to 60 years with SMA previously enrolled in Study BP29420 (MOONFISH)8 with the splicing modifier RG7800 (RO6885247) or received previous treatment with nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec-xioi (ZOLGENSMA®).

<table>
<thead>
<tr>
<th>JEWELFISH Non-naïve, aged 6 months to 60 years old (N=174)*</th>
<th>Primary endpoints</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety</td>
<td>PK/PD relationship (PD investigations will include analyses of SMN2 mRNA splice forms and SMN protein)</td>
</tr>
<tr>
<td></td>
<td>PK: Mean plasma concentration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cmax, AUC and Ctrough of risdiplam and metabolites</td>
<td></td>
</tr>
</tbody>
</table>

*Total enrolled patients (enrollment complete): 74 patients previously treated with olesoxime, 73 patients previously treated with nusinersen, 13 patients previously enrolled in the MOONFISH RG7800 study and 14 patients previously treated with onasemnogene abeparvovec (10 patients from STRONG8 and 4 patients from STR1VE10,11).
## Patients in JEWELFISH show a diversity of copy number, SMA type, ambulatory status and previous treatment

<table>
<thead>
<tr>
<th>Demographic / Previous Treatment</th>
<th>RG7800 (MOONFISH) (n=9)</th>
<th>Nusinersen (n=24)</th>
<th>Olesoxime (n=12)</th>
<th>All patients (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at screening, years, median (range)</strong></td>
<td>30.0 (16–52)</td>
<td>12.0 (2–60)</td>
<td>20.5 (11–29)</td>
<td>16.0 (2–60)</td>
</tr>
<tr>
<td><strong>Gender, female/male, n (%)</strong></td>
<td>2/7 (22.2/77.8)</td>
<td>14/10 (58.3/41.7)</td>
<td>6/6 (50.0/50.0)</td>
<td>22/23 (48.9/51.1)</td>
</tr>
<tr>
<td><strong>Risdiplam treatment duration, months, median (range)</strong></td>
<td>21.16 (17.7–24.2)</td>
<td>2.91 (0.0–28.9)</td>
<td>0.44 (0.0–1.9)</td>
<td>2.86 (0.0–28.9)</td>
</tr>
<tr>
<td><strong>SMA type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>2 (8.3)</td>
<td>0</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>2</td>
<td>5 (55.6)</td>
<td>14 (58.3)</td>
<td>9 (75.0)</td>
<td>28 (62.2)</td>
</tr>
<tr>
<td>3</td>
<td>4 (44.4)</td>
<td>8 (33.3)</td>
<td>3 (25.0)</td>
<td>15 (33.3)</td>
</tr>
<tr>
<td><strong>SMN2 copy number, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (11.1)</td>
<td>4 (16.7)</td>
<td>1 (8.3)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>3</td>
<td>2 (22.2)</td>
<td>12 (50.0)</td>
<td>4 (33.3)</td>
<td>18 (40.0)</td>
</tr>
<tr>
<td>4</td>
<td>1 (11.1)</td>
<td>3 (12.5)</td>
<td>0</td>
<td>4 (8.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (55.6)</td>
<td>5 (20.8)</td>
<td>7 (58.3)</td>
<td>17 (38.8)</td>
</tr>
<tr>
<td><strong>Motor function at baseline†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walkers, n (%)</td>
<td>6 (66.7)</td>
<td>7 (29.2)</td>
<td>0</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Sitters, n (%)</td>
<td>2 (22.2)</td>
<td>12 (50.0)</td>
<td>9 (75.0)</td>
<td>23 (51.1)</td>
</tr>
<tr>
<td>Non-sitters, n (%)</td>
<td>4 (44.4)</td>
<td>5 (20.8)</td>
<td>3 (25.0)</td>
<td>12 (26.7)</td>
</tr>
</tbody>
</table>

*At this data cut-off, no patients who had previously been treated with onasemnogene abeparvovec had yet been enrolled. †Non-sitters are defined as scoring 0 on item 9 of the MFM while sitters scored ≥1 on item 9 of the MFM but did not qualify as ambulant. Ambulant patients are defined as walkers. Data cut-off: 28 June 2019, intent-to-treat patients.
JEWELFISH: Safety and pharmacodynamic data in non-naïve patients with spinal muscular atrophy (SMA) receiving treatment with risdiplam (RG7916)

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Risdiplam treatment led to rapid and sustained increases in SMN protein levels in patients with Type 2 and 3 SMA

- SMN protein analysis from 18 patients. Analysis on new data following recruitment of additional patients is ongoing.

Error bars represent minimum and maximum values. Data cut-off: 29 May 2019.
To date,* no drug-related safety findings have led to withdrawal in any JEWELFISH patients

- Safety data is available from 45 patients exposed to risdiplam from 0–28.9 months.
- Preclinical safety findings were not observed in any patient:
  - ophthalmologic monitoring in all clinical studies of risdiplam has not shown any evidence of the retinal findings seen in preclinical monkey studies
  - hematologic parameters have remained stable over time and no drug-induced skin findings have been observed.
- 124 AEs have been reported in 26 patients:

<table>
<thead>
<tr>
<th>Most frequently reported AEs,† number of patients (%)</th>
<th>JEWELFISH (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (11)</td>
</tr>
</tbody>
</table>

*Data cut-off: 28 June 2019. †Reported in >10% of patients.
To date,* no drug-related safety findings have led to withdrawal in any JEWELFISH patients

- Two serious AEs were reported, which resolved with ongoing risdiplam treatment (femoral neck fracture, upper respiratory tract infection).
- No adverse trends have been reported after a review of all available safety laboratory results, vital signs and ECG data.
- The overall AE profile of risdiplam treatment in non-naïve patients is consistent with that in treatment-naïve patients:12,13

### Results

#### JEWELFISH patients previously treated with nusinersen (n=24)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (21)</td>
</tr>
</tbody>
</table>

#### SUNFISH Part 1 (N=51)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>27 (53)</td>
</tr>
<tr>
<td>Cough</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 (31)</td>
</tr>
</tbody>
</table>

*Data cut-off: 28 June 2019. 1Reported in >10% of patients.
†Reported in >30% of patients.
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References

7. ClinicalTrials.gov. NCT03032172 (Accessed April 2020);
8. ClinicalTrials.gov. NCT02240355 (Accessed April 2020);
9. ClinicalTrials.gov. NCT03381729 (Accessed April 2020);
10. ClinicalTrials.gov. NCT03306277 (Accessed April 2020);
11. ClinicalTrials.gov. NCT03461289 (Accessed April 2020);

Abbreviations

AEs, adverse events; AUC, area under the curve; Cmax, maximum observed plasma concentration; Ctrough, trough plasma concentration; ECG, electrocardiogram; MFM, motor function measure; PD, pharmacodynamics; PK, pharmacokinetics; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
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